US010710948B2

(12) **United States Patent**
De Lombaert et al.

(10) **Patent No.: US 10,710,948 B2**
(45) **Date of Patent: Jul. 14, 2020**

(54) **PROCESSES FOR PREPARING (R)-1-(5-CHLORO-[1,1"-BIPHENYL]-2-YL)-2,2,2-TRIFLUOROETHANOL AND 1-(5-CHLORO-[1,1"-BIPHENYL]-2-YL)-2,2,2-TRIFLUOROETHANONE**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **16/546,906**

(22) Filed: **Aug. 21, 2019**

(65) **Prior Publication Data**

US 2019/0375699 A1 Dec. 12, 2019

Related U.S. Application Data

(62) Division of application No. 15/430,786, filed on Feb. 13, 2017, now abandoned, and a division of application No. 15/059,627, filed on Mar. 3, 2016, now Pat. No. 9,611,201.

(60) Provisional application No. 62/128,652, filed on Mar. 5, 2015.

(51) **Int. Cl.**

C07C 29/32	(2006.01)
C07C 29/143	(2006.01)
C07C 259/10	(2006.01)
C07C 45/45	(2006.01)
C07C 49/80	(2006.01)

(52) **U.S. Cl.**

CPC ***C07C 29/32*** (2013.01); ***C07C 29/143*** (2013.01); ***C07C 45/455*** (2013.01); ***C07C 49/80*** (2013.01); ***C07C 259/10*** (2013.01); *C07B 2200/07* (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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(57) **ABSTRACT**

The present invention relates to processes for the preparation of (R)-1-(5-chloro-[1,1'-biphenyl]-2-yl)-2,2,2-trifluoroethanol, 1-(5-chloro-[1,1'-biphenyl]-2-yl)-2,2,2-trifluoroethanone, and intermediates thereof, which are useful in the preparation of inhibitors of TPH1 for the treatment of, for example, gastrointestinal, cardiovascular, pulmonary, inflammatory, metabolic, low bone mass diseases, serotonin syndrome, and cancer.

9 Claims, No Drawings

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PROCESSES FOR PREPARING (R)-1-(5-CHLORO-[1,1"-BIPHENYL]-2-YL)-2,2,2-TRIFLUOROETHANOL AND 1-(5-CHLORO-[1,1"-BIPHENYL]-2-YL)-2,2,2-TRIFLUOROETHANONE

CROSS-REFERENCE TO RELATED APPLICATIONS

The present application is a divisional application of U.S. Ser. No. 15/430,786, filed Feb. 13, 2017, which is a divisional application of U.S. Ser. No. 15/059,627, filed Mar. 3, 2016, which claims priority based on U.S. Provisional Patent Application No. 62/128,652, filed Mar. 5, 2015.

FIELD OF THE INVENTION

The present invention relates to processes for the preparation of (R)-1-(5-chloro-[1,1'-biphenyl]-2-yl)-2,2,2-trifluoroethanol, 1-(5-chloro-[1,1'-biphenyl]-2-yl)-2,2,2-trifluoroethanone, and intermediates thereof, which are useful in the synthesis of inhibitors of TPH1 for the treatment of, for example, gastrointestinal, cardiovascular, pulmonary, inflammatory, metabolic, low bone mass diseases, serotonin syndrome, and cancer.

BACKGROUND OF THE INVENTION

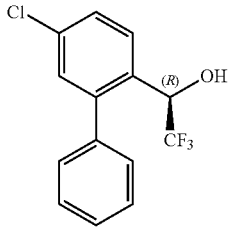
Two vertebrate isoforms of TPH, namely TPH1 and TPH2, have been identified. TPH1 is primarily expressed in the pineal gland and non-neuronal tissues, such as enterochromaffin (EC) cells located in the gastrointestinal (GI) tract. TPH2 (the dominant form in the brain) is expressed exclusively in neuronal cells, such as dorsal raphe or myenteric plexus cells. TPH catalyzes the hydroxylation of tryptophan in the biosynthesis of 5-HT. Thus, the pharmacological effects of 5-HT can be modulated by agents affecting TPH.

TPH1 inhibitors are known in the art. Spirocyclic compounds disclosed in U.S. Ser. No. 14/477,948, filed Sep. 5, 2014, can inhibit TPH1 and were found to reduce peripheral serotonin levels in animal models. The preparation of these compounds can include the coupling of an alcohol with a chloro-substituted heteroaromatic compound in the presence of base to yield an ether intermediate that can be used to make the final TPH1 inhibitor product. A particular chiral alcohol useful in the synthesis of TPH1 inhibitors is (R)-1-(5-chloro-[1,1'-biphenyl]-2-yl)-2,2,2-trifluoroethanol (see Formula A below). According to U.S. Ser. No. 14/477,948, this chiral alcohol is made by the coupling of phenyl boronic acid with (R)-1-(2-bromo-4-chlorophenyl)-2,2,2-trifluoroethanol. Alternative processes for the preparation of the compound of Formula A are provided herein.

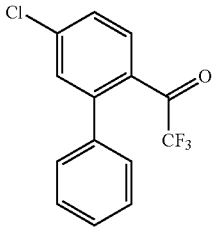
SUMMARY OF THE INVENTION

The present invention provides processes for preparing (R)-1-(5-chloro-[1,1'-biphenyl]-2-yl)-2,2,2-trifluoroethanol (Formula A) and 1-(5-chloro-[1,1'-biphenyl]-2-yl)-2,2,2-trifluoroethanone (Formula B):

A



B

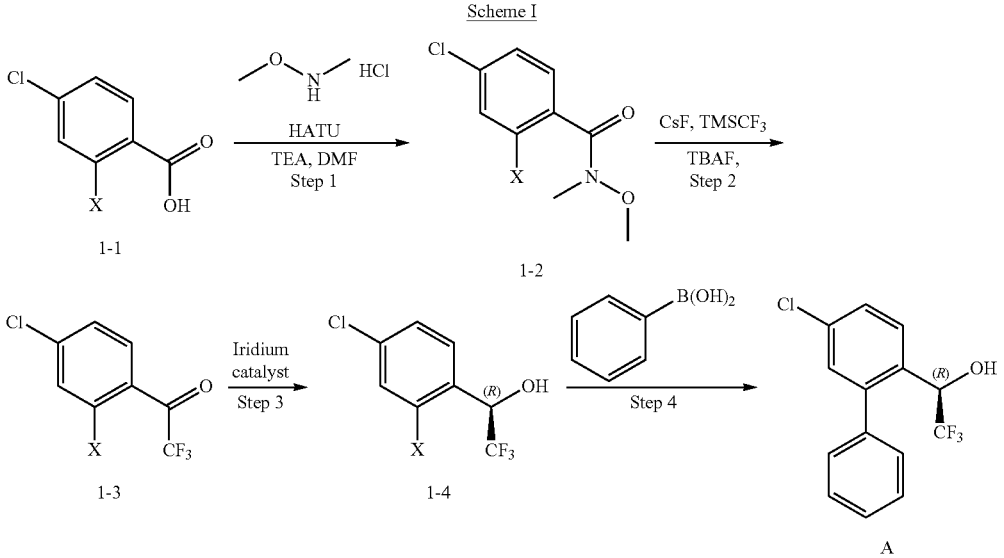


as described herein.

DETAILED DESCRIPTION

The present invention provides processes for preparing (R)-1-(5-chloro-[1,1'-biphenyl]-2-yl)-2,2,2-trifluoroethanol (Formula A) and 1-(5-chloro-[1,1'-biphenyl]-2-yl)-2,2,2-trifluoroethanone (Formula B) as set out, for example, in Scheme I, wherein X is selected from Br and I.

Scheme I



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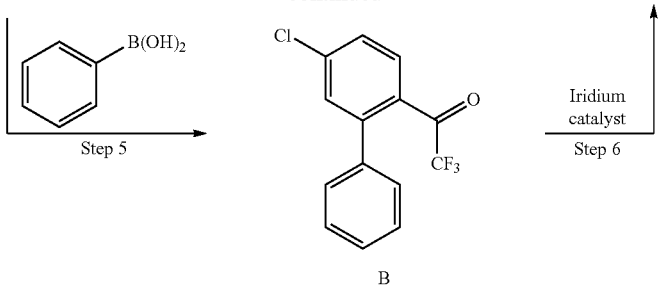
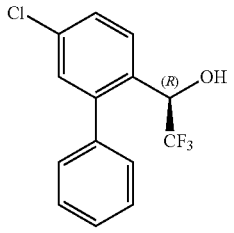


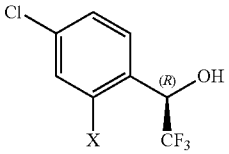
B

In some embodiments, the invention relates to a process for preparing a compound of Formula A:



A

comprising, reacting a compound of Formula 1-4:



1-4

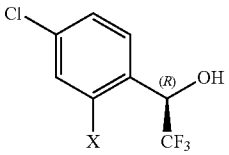
wherein X is selected from Br and I,

with phenylboronic acid to produce the compound of Formula A.

In some aspects of these embodiments, X is I. In other aspects of these embodiments, X is Br.

In some aspects of these embodiments, the reacting can be carried out under Suzuki coupling conditions such as in the presence of a Pd catalyst, for example, $Pd_2(dppf)Cl_2$. In further aspects of these embodiments, the reacting can be carried out in the presence of a solvent comprising, for example, dioxane and/or aqueous sodium carbonate. In further aspects of these embodiments, to facilitate the reacting, the coupling can be carried out at elevated temperature such as from 80 to 100° C. or at about 90° C.

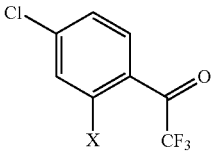
In some embodiments, the compound of Formula 1-4:



1-4

wherein X is selected from Br and I,

is prepared by reducing a compound of Formula 1-3:



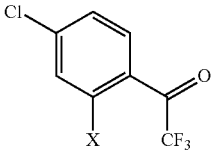
1-3

in the presence of a chiral catalyst.

In some aspects of these embodiments, X is I. In other aspects of these embodiments, X is Br.

In some aspects of these embodiments, the chiral catalyst comprises iridium such as the Ir catalyst that can be prepared by combining dichloro(pentamethylcyclopentadienyl)iridium(III) dimer with (1R, 2R)-(−)-N-(4-toluenesulfonyl)-1,2-diphenylethylenediamine. In some aspects of these embodiments, the reduction is carried out at elevated temperature such as at about 30-50° C. or at about 40° C. In further aspects of these embodiments, the reduction is carried out in the presence of formate as a reductant. The formate can be in the form of salt such as a potassium salt or sodium salt. In further aspects of these embodiments, the reduction is carried out in the presence of a solvent which, for example, can comprise acetonitrile.

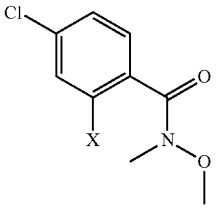
In some embodiments, the compound of Formula 1-3:



1-3

wherein X is selected from Br and I,

is prepared by combining a compound of Formula 1-2:



1-2

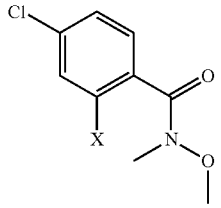
with trifluoromethyltrimethylsilane ($TMSCF_3$).

In some aspects of these embodiments, X is I. In other aspects of these embodiments, X is Br.

In some aspects of these embodiments, the combining is carried out in the presence of CsF. In further aspects of these embodiments, the combining is carried out at a reduced temperature such as at about −10 to 10° C., or at about 0° C. In further aspects of these embodiments, the combining is carried out in the presence of a solvent optionally comprising, for example, an aromatic solvent like toluene. In further aspects of these embodiments, the combining further comprises the step of adding tetra-n-butylammonium fluoride (TBAF), for example, after the compound of Formula 1-2 is combined with $TMSCF_3$.

In some embodiments, the compound of Formula 1-2:

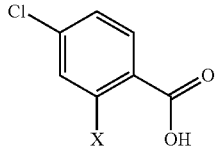
1-2



wherein X is selected from Br and I,

is prepared by coupling a compound of Formula 1-1:

1-1



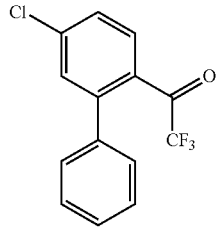
with N,O-dimethylhydroxylamine hydrochloride.

In some aspects of these embodiments, X is I. In other aspects of these embodiments, X is Br.

In some aspects of these embodiments, the coupling is carried out in the presence of a tertiary amine such as triethylamine (TEA). In further aspects of these embodiments, the coupling is carried out in the presence of a peptide coupling reagent such as (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) (HATU). In further aspects of these embodiments, the coupling is carried out using oxalyl chloride. In further aspects of these embodiments, the coupling is carried out in the presence of a solvent optionally comprising, for example, dimethylformamide (DMF), or, for example, dichloromethane (CH_2Cl_2).

In some embodiments, the invention relates to a process for preparing a compound of Formula B:

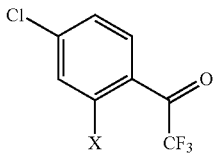
B



wherein X is selected from Br and I,

comprising reacting a compound of Formula 1-3:

1-3



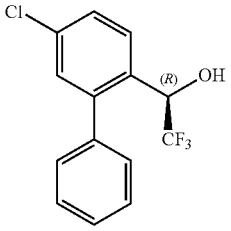
with phenylboronic acid to produce the compound of Formula B;

In some aspects of these embodiments, X is I. In other aspects of these embodiments, X is Br.

In some aspects of these embodiments, the reacting can be carried out under Suzuki coupling conditions such as in the presence of a Pd catalyst, for example, $Pd_2(dppf)Cl_2$. In further aspects of these embodiments, the reacting can be carried out in the presence of a solvent comprising, for example, dioxane and/or aqueous sodium carbonate. In further aspects of these embodiments, to facilitate the reacting, the coupling can be carried out at elevated temperature such as from 80 to 100° C. or at about 90° C.

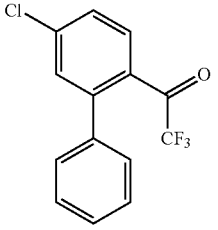
In some embodiments, the invention relates to a process for preparing a compound of Formula A:

A



comprising reducing a compound of Formula B:

B

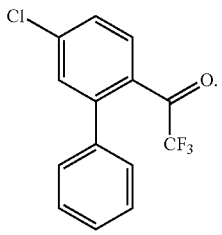


in the presence of a chiral catalyst.

In some aspects of these embodiments, the chiral catalyst comprises iridium such as the Ir catalyst that can be prepared by combining dichloro(pentamethylcyclopentadienyl)iridium(III) dimer with (1R, 2R)-(−)-N-(4-toluenesulfonyl)-1,2-diphenylethylenediamine. In further aspects of these embodiments, the reduction is carried out at elevated temperature such as at about 30-50° C. or at about 40° C. In further aspects of these embodiments, the reduction is carried out in the presence of formate as a reductant. The formate can be in the form of salt such as a potassium salt or sodium salt. In further aspects of these embodiments, the reduction is carried out in the presence of a solvent which, for example, can comprise acetonitrile.

In some embodiments, the present invention is directed to a compound of Formula A prepared by a process described herein.

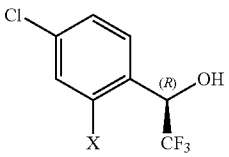
In some embodiments, the invention is directed to a compound of Formula B:



B

In some embodiments, the invention is directed to a compound of Formula B prepared by a process described herein.

In some embodiments, the invention is directed toward a compound of Formula 1-4:



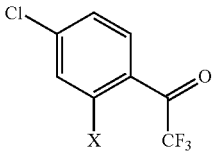
1-4

wherein X is selected from Br and I.

In some aspects of these embodiments, X is I. In other aspects of these embodiments, X is Br.

In some embodiments, the invention is directed to a compound of Formula 1-4 prepared by a process described herein.

In some embodiments, the invention is directed toward a compound of Formula 1-3:



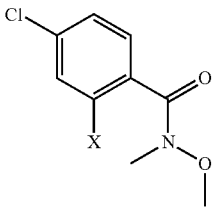
1-3

wherein X is selected from Br and I.

In some aspects of these embodiments, X is I. In other aspects of these embodiments, X is Br.

In some embodiments, the invention is directed to a compound of Formula 1-3 prepared by a process described herein.

In some embodiments, the invention is directed toward a compound of Formula 1-2:



1-2

wherein X is selected from Br and I.

In some aspects of these embodiments, X is I. In other aspects of these embodiments, X is Br.

In some embodiments, the invention is directed to a compound of Formula 1-2 prepared by a process described herein.

It is appreciated that certain features of the invention, which are, for clarity, described in the context of separate embodiments, can also be provided in combination in a single embodiment. Conversely, various features of the invention which are, for brevity, described in the context of a single embodiment, can also be provided separately or in any suitable subcombination. While certain of the processes steps are illustrated in Scheme I above, it is intended that the individual process steps may be claimed individually or in any combination. It is not intended that the processes be limited to an overall process having each and every step depicted in Scheme I.

The term "compound," as used herein, is meant to include all stereoisomers, geometric isomers, tautomers, and isotopes of the structures depicted. Compounds herein identified by name or structure as one particular tautomeric form are intended to include other tautomeric forms unless otherwise specified. Compounds herein identified by name or structure without specifying the particular configuration of a stereocenter are meant to encompass all the possible configurations at the stereocenter. For example, if a particular stereocenter in a compound of the invention could be R or S, but the name or structure of the compound does not designate which it is, than the stereocenter can be either R or S.

The term "compound," as used herein, is further meant to include all isotopes of atoms occurring in the structures depicted. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium.

In some embodiments, the compounds disclosed herein are substantially isolated. By "substantially isolated" is meant that the compound is at least partially or substantially separated from the environment in which it was formed or detected. Partial separation can include, for example, a composition enriched in the compounds of the invention. Substantial separation can include compositions containing at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% by weight of the compounds of the invention, or salt thereof.

As used herein, the phrase "elevated temperature" refers to a temperature higher than about room temperature (20-26° C.).

As used herein, the phrase "reduced temperature" refers to a temperature lower than about room temperature.

As used herein, the phrase "Suzuki coupling conditions" refers to reaction conditions that result in the formation of a carbon-carbon bond between aromatic moieties, one of which includes a halogen substituent and the other which includes a boronic acid or boronate substituent, where the reaction is carried out in the presence of a Pd(0) catalyst.

As used herein, the phrase "chiral catalyst" is a substance that pushes a reaction to favor one stereoisomer over another. In some embodiments, the chiral catalyst is a chiral coordination complex, such as a chiral coordination complex of iridium.

The present application also includes salts of the compounds described herein. In some embodiments, the salts are pharmaceutically acceptable salts which are conventional non-toxic salts of the parent compound formed, for example, from non-toxic inorganic or organic acids. Lists of suitable salts are found in *Remington's Pharmaceutical Sciences,* 17th ed., Mack Publishing Company, Easton, Pa., 1985, p.

1418 and *Journal of Pharmaceutical Science,* 66, 2 (1977), each of which is incorporated herein by reference in its entirety. The phrase "pharmaceutically acceptable" is employed herein to refer to those compounds, materials, compositions, and/or dosage forms which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of human beings and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

The processes described herein can be monitored according to any suitable method known in the art. For example, product formation can be monitored by spectroscopic means, such as nuclear magnetic resonance spectroscopy (e.g., ^{1}H or ^{13}C), infrared spectroscopy, spectrophotometry (e.g., UV-visible), or mass spectrometry; or by chromatography such as high performance liquid chromatography (HPLC) or thin layer chromatography. The compounds obtained by the reactions can be purified by any suitable method known in the art. For example, chromatography (medium pressure) on a suitable adsorbent (e.g., silica gel, alumina and the like), HPLC, or preparative thin layer chromatography; distillation; sublimation, trituration, or recrystallization. The purity of the compounds, in general, are determined by physical methods such as measuring the melting point (in case of a solid), obtaining a NMR spectrum, or performing a HPLC separation. If the melting point decreases, if unwanted signals in the NMR spectrum are decreased, or if extraneous peaks in an HPLC trace are removed, the compound can be said to have been purified. In some embodiments, the compounds are substantially purified.

Preparation of compounds can involve the protection and deprotection of various chemical groups. The need for protection and deprotection, and the selection of appropriate protecting groups can be readily determined by one skilled in the art. The chemistry of protecting groups can be found, for example, in Wuts and Greene, *Greene's Protective Groups in Organic Synthesis,* 4th Ed., John Wiley & Sons: New York, 2006, which is incorporated herein by reference in its entirety.

The reactions of the processes described herein can be carried out in suitable solvents which can be readily selected by one of skill in the art of organic synthesis. Suitable solvents can be substantially non-reactive with the starting materials (reactants), the intermediates, or products at the temperatures at which the reactions are carried out, i.e., temperatures which can range from the solvent's freezing temperature to the solvent's boiling temperature. A given reaction can be carried out in one solvent or a mixture of more than one solvent. Depending on the reaction step, suitable solvent(s) for that particular reaction step can be selected. Example solvents include water, alkanes (such as pentanes, hexanes, heptanes, cyclohexane, etc., or a mixture thereof), aromatic solvents (such as benzene, toluene, xylene, etc.), alcohols (such as methanol, ethanol, isopropanol, etc.), ethers (such as dialkylethers, methyl tert-butyl ether (MTBE), tetrahydrofuran (THF), dioxane, etc.), esters (such as ethyl acetate, butyl acetate, etc.), halogenated hydrocarbon solvents (such as dichloromethane (DCM), chloroform, dichloroethane, tetrachloroethane), dimethylformamide (DMF), dimethylsulfoxide (DMSO), acetone, acetonitrile (ACN), hexamethylphosphoramide (HMPA) and N-methyl pyrrolidone (NMP). Such solvents can be used in either their wet or anhydrous forms.

EXAMPLES

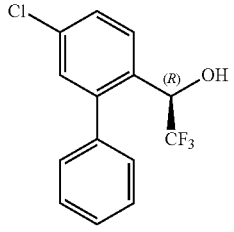
The invention will be described in greater detail by way of specific examples. The following examples are offered for illustrative purposes, and are not intended to limit the invention in any manner. Those of skill in the art will readily recognize a variety of non-critical parameters which can be changed or modified to yield essentially the same results.

^{1}H NMR Spectra were acquired on a Varian Mercury Plus 400 MHz spectrometer. For typical ^{1}H NMR spectra, the pulse angle was 45 degrees, 8 scans were summed and the spectral width was 16 ppm (−2 ppm to 14 ppm). Typically, a total of about 32768 complex points were collected during the 5.1 second acquisition time, and the recycle delay was set to 1 second. Spectra were collected at 25° C. ^{1}H NMR Spectra were typically processed with 0.3 Hz line broadening and zero-filling to about 131072 points prior to Fourier transformation. Chemical shifts were expressed in ppm relative to tetramethylsilane. The following abbreviations are used herein: br=broad signal, s=singlet, d=doublet, dd=double doublet, ddd=double double doublet, dt=double triplet, t=triplet, td=triple doublet, tt=triple triplet q=quartet, m=multiplet.

Liquid chromatography-mass spectrometry (LCMS) experiments to determine retention times and associated mass ions were performed using an Agilent Zorbax Bonus RP (reverse phase) column, 2.1×50 mm, 3.5 μm particle size, at a temperature of 50° C. and at a flow rate of 0.8 mL/min, 2 μL injection, mobile phase: (A) water with 0.1% formic acid and 1% acetonitrile, mobile phase (B) MeOH with 0.1% formic acid; retention time given in minutes. Method details: (I) ran on a Binary Pump G1312B with UV/Vis diode array detector G1315C and Agilent 6130 mass spectrometer in positive and negative ion electrospray mode with UV-detection at 220 and 254 nm with a gradient of 50-95% (B) in a 2.5 min linear gradient (II) hold for 0.5 min at 95% (B) (III) decrease from 95-5% (B) in a 0.1 min linear gradient (IV) hold for 0.29 min at 5% (B).

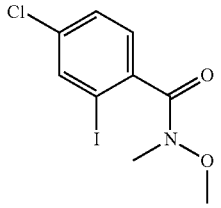
Example 1: Preparation of (R)-1-(5-chloro-[1,1'-biphenyl]-2-yl)-2,2,2-trifluoroethanol (Formula A)

A



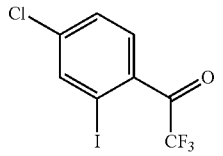
The compound of Formula A was prepared as described below (see also Scheme I above) using synthetic intermediates 1-1, 1-2, 1-3, and 1-4.

Step 1:
4-chloro-2-iodo-N-methoxy-N-methylbenzamide
(1-2, X=I)



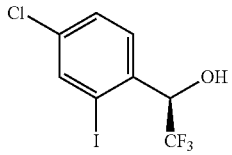
To a solution of 4-chloro-2-iodobenzoic acid (1-1, X=I) (CAS #:13421-13-1; Aldrich, SKU: 560146) (3 g, 10.62 mmol) and N,O-dimethylhydroxylamine hydrochloride (CAS #: 6638-79-5; Sigma Aldrich, SKU: D163708) (1.2 g, 12.31 mmol) in dimethylformamide (DMF) (30 mL), was added dropwise triethyl amine (TEA) (7.4 mL, 53.14 mmol), followed by the addition of (1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate) (HATU) (6.1 g, 16.05 mmol). The reaction mixture was stirred at RT for 16 h and then diluted with CH_2Cl_2 and H_2O, and the aqueous layer was extracted with CH_2Cl_2 (4×20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated in vacuo and purified by silica gel chromatography (ethyl acetate/hexanes 1:4) to afford the title compound as a white solid (3.2 g. LCMS (MH+): 325.9. ^1H NMR (400 MHz, $CDCl_3$-d): δ 3.11-3.38 (m, 3H), 3.47-3.90 (m, 3H), 7.20 (d, J=8 Hz, 1H), 7.37 (d, J=2 Hz, 1H), 7.84 (s, 1H).

Step 2: 1-(4-chloro-2-iodophenyl)-2,2,2-trifluoroethanone (1-3, X=I)



To a solution of 4-chloro-2-iodo-N-methoxy-N-methylbenzamide (1-2, X=I) (Prepared in Step 1; 1.9 g, 5.84 mmol) and CsF (222 mg, 1.46 mmol) in toluene (5 mL), was added dropwise trifluoromethyltrimethylsilane ($TMSCF_3$) (2.2 mL, 14.88 mmol) at 0° C. The reaction mixture was then warmed to RT and stirred at that temperature for 20 h. Then, water (6 mL) and tetra-n-butylammonium fluoride (TBAF) (6 mL, 1 M in THF) were added to the reaction mixture, and the reaction mixture was heated to 50° C. for 2 h. The reaction mixture was then cooled to RT and extracted with ethyl acetate (3×20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated in vacuo and purified by silica gel chromatography (100% hexanes) to provide the title compound as a yellow oil (1.39 g). LCMS (MH+): 334.9. ^1H NMR (400 MHz, $CDCl_3$-d): δ 7.51 (dd, J=10, 6 Hz, 1H), 7.37 (dd, J=10, 7 Hz, 1H), 7.84 (d, J=2 Hz, 1H).

Step 3: (R)-1-(4-chloro-2-iodophenyl)-2,2,2-trifluoroethanol (1-4)



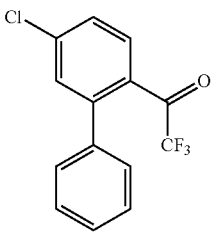
To a solution of 1-(4-chloro-2-iodophenyl)-2,2,2-trifluoroethanone (1-3, X=I) (Prepared in Step 2; 4.0 g, 11.9 mmol) in CH_3CN (20 mL) was added chiral iridium catalyst (20 mL of a 0.1 mM aqueous solution, prepared by mixing dichloro (pentamethylcyclopentadienyl)iridium(III) dimer (CAS #: 12354-84-6, 4.0 mg, 0.005 mmol) and (1R, 2R)-(−)-N-(4-toluenesulfonyl)-1,2-diphenylethylenediamine (CAS #144222-34-4, Strem Chemicals catalogue #07-2371, 3.6 mg, 0.009 mmol) in water (40 mL) and heating the resultant mixture to 40° C. for 3 h). The reaction mixture was then charged with potassium formate (HCOOK) (5.03 g, 59.80 mmol), and heated at 40° C. for 12 h. Then the reaction mixture was cooled to RT and diluted with ethyl acetate and saturated aqueous solution of NaCl. Layers were separated and the aqueous layer was extracted with ethyl acetate (4×30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo to afford the title compound as a yellow solid (4.1 g, crude) that was used in the following steps without further purification. LCMS (MH+): 336.9. ^1H NMR (400 MHz, $CDCl_3$-d): δ 3.5 (bs, 1H), 5.10 (dd, J=10 Hz, 6 Hz, 1H), 7.29 (dd, J=10, 6 Hz, 1H), 7.45 (dd, J=10, 7 Hz, 1H), 7.71 (d, J=2 Hz, 1H).

Confirmation of the (R) configuration was confirmed by Mosher Ester analysis. To a solution of (R)-1-(4-chloro-2-iodophenyl)-2,2,2-trifluoroethanol (50 mg, 0.15 mmol) in tetrahydrofuran (THF) (1 mL, anhydrous) was added 4-dimethylaminopyridine (23 mg, 0.19 mmol) and (R)-(−)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (36 μL, 0.19 mmol). The resulting mixture was stirred at room temperature for 1 h then filtered. The filtrate was concentrated and purified by preparative thin layer chromatography (TLC) (ethyl actate:hexanes/1:40) to afford (R)—(R)-1-(4-chloro-2-iodophenyl)-2,2,2-trifluoroethyl 3,3,3-trifluoro-2-methoxy-2-phenylpropanoate (50 mg, 0.09 mmol, 98% e.e. which was confirmed by ^1H NMR).

Step 4: (R)-1-(5-chloro-[1,1'-biphenyl]-2-yl)-2,2,2-trifluoroethanol (Formula A)

A solution of (R)-1-(4-chloro-2-iodophenyl)-2,2,2-trifluoroethanol (1-4) (3.1 g, 9.21 mmol), phenylboronic acid (CAS #: 98-80-6; Sigma Aldrich, SKU P20009) (1.2 g, 10.2 mmol), and $Pd(dppf)Cl_2$ (CAS #72287-26-4; Sigma Aldrich SKU: 697230) (337 mg, 0.46 mmol) in dioxane (30.0 mL) and Na_2CO_3 (10.0 mL, 2.0 M aqueous solution) was purged with N_2 three times, and the resultant reaction mixture was heated to 90° C. for 2 h. The reaction mixture was then cooled to RT and diluted with CH_2Cl_2 and water. Layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and purified by silica gel chromatography (ethyl acetate/hexanes 1/10) to afford the title compound as a white solid (2.4 g over 2 steps). ^1H NMR (400 MHz, $CDCl_3$-d): δ 3.51 (m, 1H), 5.08-5.13 (q, J=20, 7 Hz, 1H), 7.26-7.30 (m, 4H), 7.42-7.46 (m, 3H), 7.70 (d, J=8 Hz, 1H). The (R) configuration of the title product was confirmed by Mosher Ester analysis (98% e.e.) as described above for the product of Step 1: (R)-1-(4-chloro-2-iodophenyl)-2,2,2-trifluoroethanol.

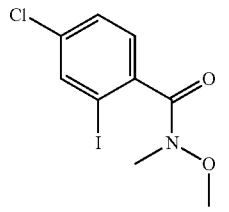
Example 2: Preparation of 1-(5-chloro-[1,1'-biphenyl]-2-yl)-2,2,2-trifluoroethanone (Formula B)



B

The compound of Formula B was prepared as described below (see also Scheme I above) using synthetic intermediates 1-1, 1-2, and 1-3.

Step 1:
4-chloro-2-iodo-N-methoxy-N-methylbenzamide
(1-2, X=I)

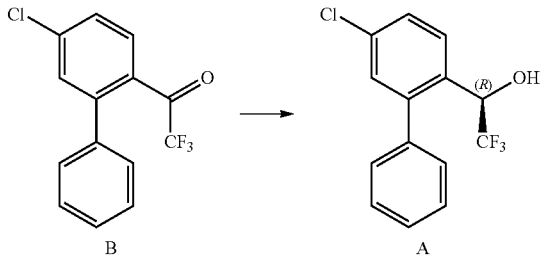


To a solution of 4-chloro-2-iodobenzoic acid (1-1, X=I) (296 g, 1.1 mol) in CH_2Cl_2 (3 L) and DMF (2 mL) was added oxalyl dichloride (266.1 g, 2.1 mol) dropwise at 0° C. over a period of 1 h. The resultant reaction mixture was stirred at 0° C. for 2 h and then concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and concentrated twice. Then the residue was dissolved in CH_2Cl_2 (1 L) and cooled to 0° C., followed by the dropwise addition of a mixture of N,O-dimethylhydroxylamine hydrochloride (Sigma Aldrich, SKU: D163708; 112.4 g, 1.15 mol) in CH_2Cl_2 (1 L) and triethyl amine (1 L, 3.15 mol) at 0° C. over a period of 1 h. The reaction mixture was then warmed to RT and stirred at that temperature for 16 h. After this time, the mixture was diluted with H_2O and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated in vacuo and purified by silica gel chromatography (ethyl acetate/hexanes 1/4) to afford the title compound (320 g) as a white solid LCMS (MH+): 325.9. ^1H NMR (400 MHz, $CDCl_3$-d): δ 3.11-3.38 (m, 3H), 3.47-3.90 (m, 3H), 7.20 (d, J=8 Hz, 1H), 7.37 (d, J=2 Hz, 1H), 7.84 (s, 1H).

Step 2: 1-(5-chloro-[1,1'-biphenyl]-2-yl)-2,2,2-trifluoroethanone (Formula B)

A solution of 1-(4-chloro-2-iodophenyl)-2,2,2-trifluoroethanone (1-3, X=I, prepared in Example 1, Step 2) (145 g, 0.43 mol), phenylboronic acid (CAS #: 98-80-6; Sigma Aldrich, SKU P20009; 55.5 g, 0.455 mol) and $Pd(dppf)Cl_2$ (CAS #72287-26-4; Sigma Aldrich SKU: 697230; 9.5 g, 0.013 mol) in dioxane (1450 mL) and Na_2CO_3 (435 mL, 2.0 M aqueous solution) was purged with N_2 and stirred at 90° C. for 2 h. After this time, the reaction mixture was cooled to RT and then diluted with H_2O. Layers were separated and the aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, concentrated in vacuo and purified by silica gel chromatography (100% hexanes) to afford the title compound (115 g) as a white solid. LCMS (MH+): 284.66. ^1H NMR (400 MHz, $CDCl_3$-d): δ 7.23-7.27 (m, 2H), 7.42-7.44 (m, 3H), 7.47-7.49 (m, 2H), 7.67-7.70 (m, 1H)

Example 3: Preparation of (R)-1-(5-chloro-[1,1'-biphenyl]-2-yl)-2,2,2-trifluoroethanol (Formula A)



B A

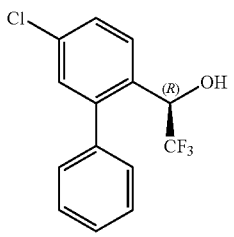
The compound of Formula A was prepared as described below (see also Scheme I above) using the compound of Formula B as synthetic starting material.

To a 22 L 3-necked reactor, fitted with a mechanical stirrer, a temperature probe, and a N_2 inlet, were charged sequentially dichloro(pentamethyl cyclopentadienyl)iridium (III) dimer ([Cp*IrCl2]2, 1.52 g, 1.90 mmol, CAS: 12354-84-6), (1R,2R)-(−)-(4-toluenesulfonyl)-1,2-diphenylethylenediamine (1.52 g, 4.15 mmol, CAS: 144222-34-4, Strem Chemicals catalogue #07-2371) and water (8 L) at RT. The resulting reaction mixture was heated to 40° C. for 3 h to provide a homogeneous orange solution. To this active catalyst solution at the current temperature (40° C.), was added potassium formate (1476 g, 17.55 mol), and a solution of 1-(2-phenyl-4-chlorophenyl)-2,2,2-trifluoroethanone (compound of Formula B prepared in Example 2) (1000 g, 3.51 mol) in CH_3CN (8 L). The reaction mixture was then stirred at 40° C. for 2 h and then cooled to RT and the layers were separated. The aqueous layer was extracted with MTBE (2×3 L) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to provide (R)-1-(2-phenyl-4-chlorophenyl)-2,2,2-trifluoroethanol (1006 g) as a thick yellow oil used without further purification.

Various modifications of the invention, in addition to those described herein, will be apparent to those skilled in the art from the foregoing description. Such modifications are also intended to fall within the scope of the appended claims. Each reference, including all patent, patent applications, and publications, cited in the present application is incorporated herein by reference in its entirety.

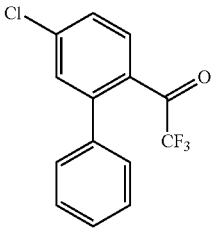
What is claimed is:

1. A process of preparing a compound of Formula A:



A

comprising reducing a compound of Formula B:



B

in the presence of a chiral catalyst.

2. The process of claim **1**, wherein said chiral catalyst comprises iridium.

3. The process of claim **1**, wherein said chiral catalyst is prepared by combining dichloro(pentamethylcyclopentadienyl)iridium(III) dimer with (1R, 2R)-(−)-N-(4-toluenesulfonyl)-1,2-diphenylethylenediamine.

4. The process of claim **1**, wherein said reducing is carried out at elevated temperature.

5. The process of claim **4**, wherein said elevated temperature is about 40° C.

6. The process of claim **1**, wherein said reducing is carried out in the presence of a formate.

7. The process of claim **6**, wherein said formate is potassium formate.

8. The process of claim **1**, wherein said reducing is carried out in the presence of a solvent.

9. The process of claim **8**, wherein said solvent comprises acetonitrile.

* * * * *